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10/008,620	12/04/2001	Ana M. Rodriguez	GC647-2	3754

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EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 03/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/008,620	RODRIGUEZ ET AL.	
	Examiner	Art Unit	
	Jon D Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-16 and 18-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-16 and 18-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. The Response filed December 23, 2003 is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

3. Claims 1-6 and 8-16 were pending. Applicants canceled claims 1-6, amended claims 8-9, 13-14, 16 and added claims 18-28. Therefore, claims 8-16 and 18-28 are pending.

Withdrawn Objections/Rejections

4. The objection to the specification is withdrawn in view of Applicants' amendments. With respect to the rejections under the second paragraph of 35 U.S.C. 112, the rejections denoted A-D, F-G are withdrawn in view of applicant's amendments to the claims and/or cancellation of claims. The statutory type (35 U.S.C. 101) double patenting rejection is withdrawn in view of Applicants' cancellation of claims. All other rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claims Rejections - 35 U.S.C. 112, second paragraph

5. Claims 8-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

E. **Claims 8, 10-12** recite the limitation "the primers" and/or "said primers" and/or "one primer" (e.g., see claim 8, step 1(c)). There is insufficient antecedent basis for this limitation in the claim. Therefore, claims 8, 10-12 and all dependent claims are rejected under 35 USC 112, second paragraph.

H. **Claims 13-14** recite the limitation "at least one mutagenic primer" (e.g., see claim 13, line 1). There is insufficient antecedent basis for this limitation in the claim. Therefore, claims 13-14 and all dependent claims are rejected under 35 USC 112, second paragraph.

I. **Claim 16** recites the limitation "said protein product" (e.g., see claim 16, line 1). There is insufficient antecedent basis for this limitation in the claim. Therefore, claim 16 and all dependent claims are rejected under 35 USC 112, second paragraph.

Response

6. Applicant's arguments directed to the above 35 U.S.C. 112, second paragraph rejections were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or newly amended arguments.

A-D. Withdrawn.

E, G. Applicants argue, "In regard to Claims 8-16, Applicants have amended the Claims to provide a more clear recitation" (e.g., see 12/23/2003 Response, page 6, last paragraph).

F. Withdrawn.

I. Applicants argue that "no amendment to the 'said protein product' recitation is needed ... [because] claim 17 depends from claim 15, which recites ...protein product." (e.g., see 12/23/2003 Response, page 7, paragraph 1).

This is not found persuasive for the following reasons:

E. First, the Examiner notes that Applicants statement that the newly amended claims, "provide a more clear recitation" is wholly unsubstantiated i.e., Applicants have not provided any rationale for this assertion. Second, the Examiner contends that the amendments have not gone far enough. For example, does the phrase "wherein one primer" refer to the "a least one primer" or the "remaining primers." If it refers to the "a least one primer" then why was the "at least" part removed? Furthermore, does the "said primers" in step (c) refer to the "a least one primer" or the "one primer" or the "remaining primers" or some combination? Therefore, there is insufficient antecedent basis for these limitations in the claim.

G. First, the Examiner notes that Applicants statement that the newly amended claims, "provide a more clear recitation" is wholly unsubstantiated i.e., Applicants have not provided any rationale for this assertion. Second, the Examiner contends that the

amendments have not gone far enough. For example, the "at least one mutagenic primer" is not referred to in either claim 8 or claim 12 to which claims 13-14 depend. Therefore, there is insufficient antecedent basis for these limitations in the claim.

I. The Examiner contends that claim 15 refers to a "desired protein product" not a "protein product" and, as a result, there is insufficient antecedent basis in the claim.

Accordingly, the 35 U.S.C. 112, second paragraph rejections cited above are hereby maintained.

Claims Rejections - 35 U.S.C. 102

7. Claims 8 and 11-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Bauer et al (US Patent No. 5,932,419) (Date of Patent is **August 3, 1999**) (IDS Paper #10).

For ***claims 8 and 12***, Bauer et al disclose a method for introducing site-directed mutations into circular DNA molecules of interest by means of mutagenic primer pairs (see Bauer et al, entire document, especially abstract), which anticipates claims 8 and 12. For example, Bauer et al disclose using a double stranded circular DNA "template" (see Bauer et al, column 2 lines 42-45; see also column 5, lines 56-57; see also column 6, line 36 showing that single stranded DNA may also be used as templates), which anticipates "obtaining a template nucleic acid" in claim 8(a). Furthermore, Bauer et al disclose the use of mutagenic primer "pairs" that contain at least one mutation site with respect to the target sequence (see Bauer et al, abstract; see also column 2, lines 44-46; see also column 4 lines 37-47; see also column 6, last paragraph). In addition, Bauer et al disclose that the

primers can be in "opposite orientation" (see Bauer et al, figure 1B wherein arrows show an "opposite orientation"; see also column 4, line 13; see also column 5, line 53).which anticipates claim 8 (b) and (c) and claim 12 (please note that Applicants' use of "comprising" terminology does not preclude the use of more than one mutagenic primer). Bauer et al disclose hybridizing said "mutagenic" primer pairs to the target sequence (see Bauer et al, column 2, lines 51-52), which anticipates claim 8 (c). Furthermore, Bauer et al disclose the production of more than one mutant strand (i.e., a library of mutant template nucleic acids) via linear cyclic amplification reactions (see Bauer et al, column 2, last paragraph; see especially line 56 and lines 61-62; see also column 7, last paragraph and column 8), which anticipates claim 8 (d).

For ***claims 11***, Bauer et al disclose first and second oligonucleotides at a concentration of 100 ng/ul (see Bauer et al, column 12, lines 47 and 49), which anticipates claim 3 because 100 ng/ul is less than saturation concentration.

For ***claims 13-14***, Bauer et al disclose "substitutions, insertions and deletions" that are "well known" to persons of skill in the art wherein the mutagenic primers contain "one or more mutagenic sites" (see Bauer et al, column 7, paragraph 1; see also column 6, line 57-58).

For ***claims 15-16***, Bauer et al disclose a template strand that corresponds to the lacZ protein product i.e., β-galactosidase enzyme (see Bauer et al, column 12, "EXAMPLES").

Response

8. Applicant's arguments directed to the above 35 U.S.C. § 102 rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "Unlike the presently claimed invention, the Bauer et al. reference teaches the use of one primer pair, in which the primers are complementary (at least partially) to each other. Furthermore, these primers are both mutagenic primers. In contrast, the presently claimed invention does not require the use of mutagenic primer pairs. Rather, as in amended claim 8, only one of the primers used is mutagenic" (e.g., see 12/23/2003 Response, page 7, paragraphs 3-4).

[2] Applicants further argue, "because the dependent claims incorporate all of the elements of the independent claims, the dependent claims are likewise not anticipated by the Bauer et al. Patent" (e.g., see 12/23/2003 Response, page 7, last paragraph).

This is not found persuasive for the following reasons:

[1] The Examiner contends that Applicants arguments are not commensurate in scope with Applicants claims. First the limitation that the primers cannot be "complementary (at least partially) to each other" is nowhere recited in Applicants' claims. Second, Applicants' use of "comprising" terminology does not preclude the possibility that more than one primer may be used i.e., the claims do not state that "only one" primer can be used. Furthermore, it is not clear

what primer is being referred to in the claims (e.g., see 35 U.S.C. 112, second paragraph rejections).

[2] The Examiner contends that the independent claims are anticipated (see section [1] above) and, as a result, Applicants arguments are moot.

Accordingly, the 35 U.S.C. 102 rejection cited above is hereby maintained.

Claim Rejections - 35 USC § 103

9. Claims 8-16 and 18-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bauer et al (US Patent No. 5,932,419) (Date of Patent is **August 3, 1999**) and Stemmer et al (US Patent No. 5,512,463) (Date of Patent is **April 30, 1996**) (IDS Paper # 10).

For ***claims 8, 12, 23***, Bauer et al disclose a method for introducing site-directed mutations into circular DNA molecules of interest by means of mutagenic primer pairs (see Bauer et al, entire document, especially abstract), which reads on claims 8 and 12. For example, Bauer et al disclose using a double stranded circular DNA "template" (see Bauer et al, column 2 lines 42-45; see also column 5, lines 56-57; see also column 6, line 36 showing that single stranded DNA may also be used as templates), which reads on "obtaining a template nucleic acid" in claim 8(a). Furthermore, Bauer et al disclose the use of mutagenic primer "pairs" that contain at least one mutation site with respect to the target sequence (see Bauer et al, abstract; see also column 2, lines 44-46; see also column 4 lines 37-47; see also column 6, last paragraph). In addition, Bauer et al disclose that the

primers can be in "opposite orientation" (see Bauer et al, figure 1B wherein arrows show an "opposite orientation"; see also column 4, line 13; see also column 5, line 53), which reads on claim 8 (b) and (c), claim 12 and claim 23 (please note that Applicants' use of "comprising" terminology does not preclude the use of more than one mutagenic primer). Bauer et al disclose hybridizing said "mutagenic" primer pairs to the target sequence (see Bauer et al, column 2, lines 51-52), which reads on claim 8 (c). Furthermore, Bauer et al disclose the production of more than one mutant strand (i.e., a library of mutant template nucleic acids) via linear cyclic amplification reactions (see Bauer et al, column 2, last paragraph; see especially line 56 and lines 61-62; see also column 7, last paragraph and column 8), which reads on claim 8 (d).

For ***claims 11, 22***, Bauer et al disclose first and second oligonucleotides at a concentration of 100 ng/ul (see Bauer et al, column 12, lines 47 and 49), which reads on claim 3 because 100 ng/ul is less than saturation concentration.

For ***claims 13-14, 24-25***, Bauer et al disclose "substitutions, insertions and deletions" that are "well known" to persons of skill in the art wherein the mutagenic primers contain "one or more mutagenic sites" (see Bauer et al, column 7, paragraph 1; see also column 6, line 57-58), which reads on claims 13-14 and 24-25.

For ***claims 15-16, 26-27***, Bauer et al disclose a template strand that corresponds to the lacZ protein product i.e., β-galactosidase enzyme (see Bauer et al, column 12, "EXAMPLES"), which reads on claims 15-16 and 26-27.

The prior art teaching of Bauer et al differs from the claimed invention as follows:

For ***claims 9, 19-20 and 28***, the prior art teaching of Bauer et al is deficient in that it does not teach the use of 3 to 15 primers or 4 to 7 primers.

For ***claims 10, 21***, the prior art teaching of Bauer et al differs from the claimed invention by not specifically reciting the use of "discontiguous" primers. Bauer et al only teaches the use of "overlapping" or "partially overlapping" primers (e.g., see Bauer et al, column 7, lines 10-12).

However, Stemmer et al teaches the following limitations that are deficient in Bauer et al:

For ***claims 9, 19-20 and 28***, Stemmer et al disclose a specific example of four primers wherein position 6 contains G and A and the complementary primer contains C and T producing a total of four primers. Stemmer et al also provides a general teaching that would allow a person of skill in the art to immediately envision any number of primers (e.g., see Stemmer et al, column 18, paragraph 1).

For ***claims 10, 21***, Stemmer et al (see entire document) teach that the primers are discontiguous (see Stemmer et al, column 17, lines 30-31 "The primers may be ... non-overlapping").

It would have been obvious to one skilled in the art at the time the invention was made to replace the "exponential" amplification (i.e., PCR) method as taught by Stemmer et al for making combinatorial nucleic acid libraries with the "linear" amplification as taught by Bauer et al because Bauer et al explicitly states that "linear" amplification is better than "exponential" amplification because it does not require a "ligation" step which would "reduce the time and expense required to carry out ... conventional methods of site

directed mutagenesis" (see Bauer et al, column 11, lines 36-40). Consequently, one of ordinary skill in the art would have been motivated to use the "linear" amplification as taught by Bauer et al "to reduce the time and expense" for generating libraries and transforming host cells as mentioned above. Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because Stemmer et al teaches that both "overlapping" and "non-overlapping" primers can be used to generate the nucleic acid libraries which would encompass the "overlapping" primers or "partially overlapping" primers disclosed by Bauer et al (see Bauer et al, column 7, lines 10-12).

Response

10. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "as indicated above, there is nothing in the Bauer et al. Patent that teaches or even remotely suggests the presently claimed invention" (see 12/23/2003 Response, pages 8-9, especially page 9, paragraph 2, first sentence).

[2] Applicants argue, "Although Stemmer et al. teaches the use of 'primer populations' (See, col. 17, lines 19-31) that can include primers that overlap on the template, are contiguous or discontiguous, Stemmer et al. fail to teach a method in which at least two primers are used, wherein one primer is in opposite orientation to the remaining primers and at least one primer is

a mutagenic primer that corresponds to a desired mutation. The definition of 'primer population' in Stemmer et al. (See, col. 17, lines 19-31) indicates that the term 'is used to describe the pool of primers that have identical base compositions except at certain predetermined locations along the sequence that contain a variable composition.' In contrast the presently claimed invention does not rely on the use of 'primer populations.' Rather, the primers used in the presently claimed invention are designed such that at least to primers are mixed, one of which is a mutagenic primer and at least one is in the opposite orientation to the remaining primers. In the Stemmer et al. Patent, the two primer populations are oriented in opposite directions. Thus, there is no teaching in the Stemmer et al. Patent of the primers used in the methods presently claimed." (see 12/23/2003 Response, page 9, paragraph 2).

This is not found persuasive for the following reasons:

[1] The Examiner contends that Applicants statement is wholly unsubstantiated because Applicants have not provided and rationale to maintain this assertion. Applicants state that their rationale was "indicated above", but the previous five paragraphs just summarize the Examiner's rejection i.e., no rationale for this assertion is provided. If Applicants intend the "indicated above" section to refer to the "The Claims are Novel" section on pages 7-8, then the Examiner contends that these arguments were sufficiently addressed in the 35 U.S.C. § 102(b) rejection/Response above.

[2] In response to applicant's arguments against the Stemmer et al. reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

Non-Statutory Double Patenting

11. Claims 8-16 and 18-28 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent Application No. 20020155439 A1 (referred to as '439) in view of Bauer et al (US Patent No. 5,932,419) (Date of Patent is **August 3, 1999**) and Stemmer et al (US Patent No. 5,512,463) (Date of Patent is **April 30, 1996**).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examiner application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1986).

Here, claims 1-6 of '439 recite the exact same method steps as those claimed by Applicants with the exception that the method of claims 1-6 in '439 fail to disclose primers between 3 to 15 primers (e.g., see claim 1 of '439 wherein [a] obtaining a template nucleic acid is disclosed, [b] preparing a first oligonucleotide corresponding to a first desired mutation, [c] mixing the oligonucleotides so as to hybrdize said oligonucleotides to the template, [d] subjecting the mixture to linear cyclic amplification; see also claim 2 wherein "discontiguous" primers are disclosed; see also claim 3 wherein saturation concentration is disclosed; see also claims 5-6 wherein an enzyme "desired protein product is disclosed). However, the combined

teachings of Bauer et al and Stemmer et al teach between 3 to 15 primers and all other limitations for claims 8-16 and 18-28 (see 35 U.S.C. § 103(a) rejection above, which is incorporated in its entirety herein by reference). It would have been obvious to modify the method of claims 1-6 of '439 to use the between 3 to 15 primers as taught by the combined teachings of Bauer et al and Stemmer et al because the combined teachings of Bauer et al and Stemmer et al falls within the scope of the claims 1-6 of '439 (i.e., the references represent analogous art) and the combined teachings of Bauer et al and Stemmer et al explicitly state that their exemplified embodiments will "reduce the time and expense" (see Bauer et al, column 7, lines 10-12).

This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Response

12. Applicant's arguments directed to the above double patenting rejection were fully considered but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicants argue, "upon receiving notification of allowance of the claims, applicants will provide a terminal disclaimer to remove the obviousness-type double patenting rejection" (e.g., see 12/23/2003 Response, page 10, last paragraph).

This is not found persuasive for the following reasons:

The Examiner contends that Applicants have acknowledged their duty to file a terminal disclaimer (see above), but have failed to do so. Consequently, the double patenting rejection is a maintained.

Accordingly, the double patenting rejection cited above is hereby maintained.

New Rejections

Claims Rejections - 35 U.S.C. 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 8 is rejected under 35 U.S.C. 112, first paragraph, as containing subject mater which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (New Matter).

Newly amended claim 8 recites, "producing a library of mutant nucleic acid molecules ... wherein one primer is mutagenic and corresponds to a desired mutation" (see newly amended claim 8). The Examiner does not find support for producing a library using only one mutagenic primer. If applicant believes this rejection is in error, applicant must disclose where in the specification support for this amendment can be found in accordance with MPEP 714.02. Therefore, claim 8 and all claims from which 8 depends represent new matter.

Claims Rejections - 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 8-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. For **claim 8**, the claim is vague and indefinite because it is not clear how a "library" of nucleic acid molecules can be produced using ONLY "one" mutagenic primer and only "one" template strand i.e., this will produce only one mutant because the other "non-mutagenic" primers will produce the same template strand. If a library is produced, the Examiner contends that the claim is incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: method steps that will facilitate "more than one" nucleic acid molecule that will result in the production of a library. Applicants are requested to clarify and/or correct. Therefore, claim 8 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

B. For **claim 12**, the claim is vague and indefinite because it is not clear how the limitation "wherein all said primers in step (b) are mutagenic primers" further limits the claim. According to Applicants, "ONLY ONE" of the primers used is mutagenic (e.g., see 12/23/2003 Response, page 7, last paragraph, "In contrast, the presently claimed invention does not require the use of mutagenic primer pairs. Rather, as in amended claim 8, only one of the primers used is mutagenic") (emphasis added). If Applicants statement is true then claim 12 which is drawn to "more than one" mutagenic primer does not further limit the claim. Applicants are requested to clarify and/or correct.

Therefore, claim 8 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

Claims Rejections - 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(e) the invention was described in-
(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

15. Claims 8-16 and 18-28 are rejected under 35 U.S.C. 102(e) as being anticipated by Caldwell et al (U.S. Patent No. 6,582,914) (Filing Date is ***October 26, 2000***).

For ***claims 8 and 19***, Caldwell et al (see entire document) disclose methods for generating a library of oligonucleotides comprising a controlled distribution of mutations (see Caldwell et al, abstract), which anticipates claim 8, 19. For example, Caldwell et al disclose, **[a]** "obtaining a template nucleic acid" (e.g., see Caldwell et al, claim 1, step (a)). In addition, Caldwell et al disclose **[b]** preparing a first and second oligonucleotide corresponding to a first and second desired mutation within said template nucleic acid and allowing them to hybridize to a template (e.g., see Caldwell et al, claim 1, step (c); see also figures 1-2; see also Summary of the Invention) (Please note that applicants'

"comprising" terminology does not preclude the use of more than one mutagenic primer). Furthermore, Caldwell et al disclose that the first and second oligonucleotide can be non-complementary (e.g., see Caldwell et al, figures 1-2 showing non-complementary primers; see also Summary of invention). Finally, Caldwell et al disclose **[c-d]** allowing said primers to hybridize to the template nucleic acid to produce a mixture and subjecting said mixture to linear cyclic amplification to produce a library of mutant template nucleic acids (e.g., see Caldwell et al, column 11, lines 25-26, "long products increases linearly because they are produce only from the original nucleic acid"; see also claim 1; see also Summary of Invention). Caldwell et al. disclose the use of multiple primers including 4 primers (e.g., see figure 1, wherein primers A-D are used), which reads on claim 19.

For ***claims 9, 18, 20 and 28***, Caldwell et al. disclose the use of multiple primers including 4 primers (e.g., see figure 1, wherein primers A-D are used).

For ***claims 10 and 21,*** Caldwell et al disclose oligonucleotides that are discontiguous (e.g., see Caldwell et al, lines 26-31; see also figures 1-2; see also Summary of Invention).

For ***claims 11 and 22***, Caldwell et al disclose oligonucleotides that are present in less than saturating conditions (e.g., see Caldwell et al, claim 1, step (e)).

For ***claim 12 and 23***, Caldwell et al further disclose the use of all mutagenic primers "and/or" the use of non-mutagenic primers in various ratios (e.g., see Caldwell et al, abstract; see also claim 7).

For ***claims 13-14 and 24-25***, Caldwell et al further disclose at least one mutagenic primer encoding 1 to 4 amino acid mutations and at least one mutagenic primer

comprising 1 to 12 nucleotide mutations (e.g., see Example 1, see especially SEQ ID No. 1 and Tables 2 and 3).

For ***claims 15-16 and 26-27***, Caldwell et al disclose protein products selected from an enzyme, hormone, vaccine, antibody, etc. (e.g., see Caldwell et al, claim 5).

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
March 11, 2004